SPECIAL ARTICLES

Vitamin E and Its Relation to Heart Disease

By ROBERT E. OLSON, M.D.

SUMMARY

Although vitamin E deficiency in ruminants results in conspicuous heart disease, a similar deficiency state in primates appears to spare the heart, even when other systems are affected. No heart disease in man has been related to a vitamin E deficiency. The pharmacologic use of vitamin E in doses 10 to 50 times the daily requirement was recommended in 1947 for the treatment of a variety of cardiovascular disorders, including intermittent claudication, angina pectoris, coronary occlusion, congestive heart failure, thrombophlebitis and thromboembolism, but no evidence of its effectiveness has been convincingly verified during the ensuing 25 years.

VITAMIN E is one of the four fat-soluble vitamins required by animals for normal cell differentiation and function. Unlike the water-soluble vitamins of the B-complex, these lipid-vitamins are not required by microorganisms and most living forms, but express their physiological functions in higher vertebrates.

Vitamin E was discovered by Evans and Bishop1 in 1923 in studies of fertility in female rats. They found that diets fortified with the two then known fat-soluble vitamins (A and D) would not permit pregnant rats to carry their young to term. Instead, these rats would abort and the fetus would be resorbed, demonstrating the so-called resorption-gestation syndrome. A study of fats and oils which would prevent this syndrome revealed that wheat germ oil and other vegetable oils were good sources of the new factor. Cod liver oil contained only small amounts. Because of its role in fertility in the rat, the new substance was named tocopherol, literally the substance required to “assure normal births.”

Additional Indexing Words:
Vitamin E Cardiovascular disease
Intermittent claudication Angina pectoris
Thrombophlebitis Thromboembolism

Myocardial infarction Myocarditis
Coronary occlusion Congestive heart failure

Chemistry of the Tocopherols

In 1936, d-α-tocopherol was isolated by Evans and his colleagues2 from the non-saponifiable fraction of wheat germ oil. In 1938, its chemical structure was determined to be that of substituted chromanol shown below3 and this structure was confirmed by synthesis in the same year.4

The d-isomer is the natural form, and is the most potent of all tocopherols in biological assays. Other companion tocopherols (β, γ, δ and the related tocotrienols) occurring in fats and oils vary from the α-homologue in the extent and position of methylation on the ring and in the degree of unsaturation of the side chain. In α-tocopherol, the isoprenyl side chain is fully saturated.

One international unit is equivalent to the biological activity of 1 mg of synthetic dl-α-tocopherol acetate when administered to whole animals. It must be recognized, however, that the esters of tocopherol are not active as such, but must be hydrolyzed in the body to yield the free phenol.

Vitamin E Deficiency Diseases in Animals

In contrast to diseases caused by the lack of most essential nutrients, the diseases caused by a deficiency of vitamin E vary widely from animal to animal and involve a variety of systems in different species. Disorders of reproduction, of muscle function, of the vascular system, including blood
and bone marrow, of the brain, and of the liver have been observed separately and together in various species deprived of vitamin E. Table 1 presents the wide spectrum of manifestations of vitamin E deficiency. Defective embryogenesis as well as resorption-gestation is observed in a number of species. Exudative diathesis, a disorder of capillary permeability, is seen only in poultry. Skeletal muscle dystrophy is noted in a number of species, but only in certain species is this accompanied by cardiomyopathy. In ruminants, the cardiac disease is severe, in rabbits mild, and in primates non-existent. Hemopoiesis is affected only in monkeys and pigs, and hepatic necrosis occurs only in rats and pigs. This bewildering and unpredictable array of manifestations of vitamin E deficiency in animals and birds has not assisted in generating a functional view of the vitamin's function at the cellular, to say nothing of the molecular level.

There is another feature of vitamin E action which further complicates an analysis of its action at the cellular and subcellular level. That feature is its partial or complete replaceability by nontocopherols, including selenium, usually given as selenite (SeO\textsubscript{3}\textsuperscript{2−}), ubiquinones and ubichromanols, the sulphur amino acids methionine and cystine, and organic antioxidants such as diphenylphenylene-diamine (DPPD) and guinolines such as santoquin. The extent to which replaceability occurs depends on the species and the particular disorder induced by lack of vitamin E. These interactions are shown in Table 2. The first four diseases, encephalomalacia in poultry, abortion-resorption in rats, erythrocyte hemolysis and ceroid pigmentation in various animals, which are the result of peroxidation of lipids, appear to respond to antioxidants such as ethoxyquine or DPPD. Some investigators argue that the chemical antioxidant is protecting residual amounts of vitamin E, but regardless of mechanism the antioxidant responsive diseases are greatly improved by antioxidants. It must be remembered that the tocopherols have antioxidant properties themselves and are required in higher amounts when pro-oxidant nutrients such as polyunsaturated fatty acids are added to the diet.\textsuperscript{5}

The second group of disorders, muscle dystrophy in rabbits, guinea pigs, monkeys and chicks and testicular degeneration in the male rat, appear to respond only to vitamin E and not selenium. Strangely, the dystrophy in the chick is also prevented by cystine or methionine.\textsuperscript{6}

The third group of diseases respond better to selenium in micrograms per kilogram diet than to vitamin E in milligrams per kilogram of diet. These are the dystrophies in ruminants and in the turkey (white muscle disease) and the defect in embryogenesis in the cow.

Finally, hepatic necrosis and exudative diathesis respond to both vitamin E and selenium.

Table 1

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<tr>
<th>Vitamin E Deficiency Diseases by System Involved</th>
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<tbody>
<tr>
<td>I. Reproductive system</td>
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<tr>
<td>A. Abortion-resorption in female animals</td>
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<td>B. Testicular degeneration in male animals</td>
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<tr>
<td>II. Muscular system</td>
</tr>
<tr>
<td>A. Skeletal muscular dystrophy (rabbit, guinea pig,</td>
</tr>
<tr>
<td>monkey, duck, mouse, mink, lamb, calf, kid,</td>
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<tr>
<td>turkey, chicken, man)</td>
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<tr>
<td>B. Cardiomyopathy (lamb, calf, kid, turkey, rabbit)</td>
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<tr>
<td>III. Vascular system</td>
</tr>
<tr>
<td>A. Defective embryogenesis (rat, hen, turkey, cow,</td>
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<td>ewe)</td>
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<tr>
<td>B. Exudative diathesis (chicken, turkey)</td>
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<tr>
<td>C. Erythrocyte hemolysis (rat, chick, man)</td>
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<tr>
<td>D. Bone marrow failure (monkey)</td>
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<td>IV. Hepatobiliary system</td>
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<tr>
<td>A. Hepatic necrosis (rat, pig)</td>
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<tr>
<td>V. Central nervous system</td>
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<tr>
<td>A. Encephalomalacia (chick)</td>
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Table 2

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<tr>
<th>Interaction of Vitamin E with Other Nutrients in the Treatment of Various Deficiency Diseases</th>
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<tbody>
<tr>
<td>I. Antioxidant-responsive diseases</td>
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<tr>
<td>A. Encephalomalacia (chicks, turkeys)</td>
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<tr>
<td>B. Abortion-resorption (rats)</td>
</tr>
<tr>
<td>C. Erythrocyte hemolysis (rats, man)</td>
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<tr>
<td>D. Ceroid pigmentation (rats, mink, pigs)</td>
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<tr>
<td>II. Principally vitamin E-responsive diseases</td>
</tr>
<tr>
<td>A. Muscular dystrophy (rabbits, guinea pigs, monkeys, chicks)</td>
</tr>
<tr>
<td>B. Testicular degeneration (rat)</td>
</tr>
<tr>
<td>III. Principally selenium-responsive diseases</td>
</tr>
<tr>
<td>A. Embryogenesis defect (cow)</td>
</tr>
<tr>
<td>B. Muscle dystrophy (lamb, calf, kid, turkey)</td>
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<tr>
<td>IV. Vitamin E and selenium-responsive diseases</td>
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<tr>
<td>A. Hepatic necrosis (rat, pig)</td>
</tr>
<tr>
<td>B. Exudative diathesis (chicken)</td>
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Myocardial Lesions in Vitamin E Deficiency

Despite the common occurrence of skeletal muscle dystrophy in vitamin E deficient animals, involvement of the heart is less common and less severe. Nonetheless, there are reports in lambs and cows, as indicated earlier, that cardiac disease can occur with both functional and pathological expression including electrocardiographic changes and sudden death as shown by Draper, James and Johnson7 and Gullickson and Calverley.8 Gatz and Houchin9 observed the following sequence of events in the myocardium of deficient rabbits: increased oxygen consumption, appearance of constriction bands, hyalization of the fibers and development of basophilia, appearance of fluid drops in the cytoplasm, and onset of necrosis. Electrocardiographic changes have been variable. In rats and pigs, cardiograms have been normal with advancing skeletal dystrophy whereas species more susceptible to cardiomyopathy such as sheep, cattle and rabbits, have in some cases revealed ECG changes. In deficient rabbits, a right axis deviation was observed, accompanied by changes in the T waves. In ruminants, sudden onset of ventricular tachycardia and fibrillation has been noted. On the other hand, in severely vitamin E deficient monkeys with skeletal dystrophy and bone marrow failure, there was no cardiac involvement.10 In none of the conditioned vitamin E deficiencies in man has cardiac involvement been noted.

Mode of Action of Vitamin E

The mode of action of vitamin E at the molecular level is not known with certainty. At present, there are three hypotheses which are under continuing investigation. These are (1) the antioxidant hypothesis, (2) the respiratory chain hypothesis, and (3) the genetic regulation hypothesis.

The antioxidant hypothesis postulates that alpha-tocopherol is a physiological antioxidant which is designed to protect polyunsaturated fatty acids and other easily oxidizable groups (such as sulfhydryl groups) in tissues against the effect of oxygen which occurs in tissues at a PO2 of 10 to 20 mm of mercury and is required as a terminal electron acceptor in energy metabolism. The evidence in support of this theory is (a) that some other antioxidants including selenium salts may supplant tocopherol in preventing some of the manifestations of deficiency disease,11 (b) that some metabolites of tocopherol have been isolated which are consistent with the dimerization of an electron deficient species which would result from donation of a hydrogen atom to terminate the autocatalytic peroxidation sequence,12 (c) that polyunsaturated fatty acids which are pro-oxidants increase the alpha-tocopherol requirement,13,14 and (d) that the products of peroxidation such as ceroid pigments accumulate in tissues from vitamin E deficient animals.

The respiratory chain hypothesis postulates that alpha-tocopherol plays a specific role in electron transport in mitochondria by serving as a catalyst for respiration15 or by regulating specific enzyme and cofactor concentrations in mitochondria. K. Schwarz has been the main proponent of this hypothesis on the basis of extensive studies of mitochondria from animals undergoing hepatic necrosis from selenium or vitamin E-lack.16 A decline in respiratory capacity of mitochondria from such animals, which is partially reversed by antioxidants in vitro, and is associated with reduced lipoyl dehydrogenase and NADH oxidase, has been observed. This hypothesis has the fewest adherents at the present time.

Finally, the genetic regulation hypothesis for vitamin E was proposed by Olson in 1967.17 The essence of this theory is that alpha-tocopherol regulates in some way the transfer of genetic information from the chromosomes to the whole cell. This implies that vitamin E regulates the synthesis of specific proteins and enzymes required in the differentiation or adaptation of given tissues. The evidence for this hypothesis is (a) defects in embryogenesis and cellular proliferation are observed in the absence of vitamin E, (b) alteration in sexuality and morphology has been produced pharmacologically in the rotifer Asplanchna, a carnivorous metazoan,18 (c) some of the vitamin E deficiency syndromes are related to genetic diseases that are clearly the result of abnormal genes (muscular dystrophy, habitual abortion, Klinefelter's syndrome), (d) DNA and RNA turnover are altered in dystrophic muscle of vitamin E deficient rabbits,19 (e) the contractile protein, myosin, from vitamin E deficient dystrophic rabbits is altered in its primary structure to a more fetal type,20 (f) other fat-soluble vitamins appear to function in a similar capacity, i.e., control specific protein synthesis in the highly differentiated vertebrate.21

If a unitary theory of alpha-tocopherol action is finally established, only one of these three hypotheses can be correct. It may be however, as in the case of vitamin A, the steroid hormones, and insulin, vitamin E may have several actions at the molecular level.
Vitamin E Deficiency in Man

Vitamin E deficiency is rare in human subjects. The fact that it has never been seen as a primary deficiency disease in otherwise healthy children or adults suggests very strongly that the amount of vitamin E ordinarily present in mixed foodstuffs is adequate for maintenance of health. The recommended daily allowances for vitamin E given by the Food and Nutrition Board, N.R.C.22 ranged between 5 I.U. for infants to 30 I.U. for young adult males. Dietary surveys in this country indicate that the actual intake of tocopherols is within the range of the RDAs, i.e., 5-10 mg/1000 calories.

Premature infants23 and children with malabsorption syndromes and steatorrhea,24 celiac disease, α-β-lipoproteinemia, fibrocystic disease of the pancreas, biliary atresia, have been shown to have one or more signs of vitamin E deficiency, i.e., low plasma vitamin E levels, enhanced hydrogen peroxide hemolysis, creatinuria, ceroid pigmentation and necrosis of striated muscle. In protein-calorie malnutrition, the plasma vitamin E levels are generally low, enhanced in vitro hydrogen peroxide hemolysis is present, creatinuria may be exaggerated, and occasionally muscle weakness and necrosis out of proportion to the effects of protein-calorie malnutrition per se are noted.25 Since most of these illnesses are due to abnormalities in the absorption and transport of lipids generally, parenteral vitamin E is required to correct the deficiency state.

Pharmacologic Use of Vitamins

The old question of why some essential nutrients given in doses far exceeding the daily requirement can have special physiologic effects is not fully understood. It is true, however, that beneficial effects have been observed from the administration of vitamins in doses 10 to 100 times their ordinary requirement. A familial hypochromic microcytic anemia has been shown to respond only to pharmacologic doses of pyridoxine (25 to 200 mg/day).26 Since the signs of this disease are similar to the anemia seen in bona fide pyridoxine deficiency (usually cured with 2 mg/day of pyridoxine), it may be suspected that the dissociation constant for one of the pyridoxal-phosphate dependent enzymes active in heme synthesis is altered, or the phosphorylating enzyme for pyridoxal is defective. A similar argument has been advanced for the effectiveness of large doses of nicotinic acid in certain types of dementia.27 Nicotinic acid is also hypocholesterolemic in doses about 1000 times the daily requirement. Pauling has recently advocated the daily intake of gram quantities of vitamin C (100 times the recommended daily requirement) as a preventative for the common cold.28, 29 A general argument for the use of large doses of naturally occurring substances in genetic and even acquired diseases has been advanced by Pauling under the rubric of "orthomolecular medicine."30

Steroid hormones, which are normally synthesized by the body in physiologic amounts, have also proven effective in the treatment of selected disorders at doses 10 to 50 times the estimated daily secretion rate. The classic example is the use of corticoids in the treatment of rheumatoid arthritis and related collagen diseases.31

As regards the fat-soluble vitamins, both vitamins A and D have been used in pharmacologic doses to treat specific disorders. Vitamin D in doses of 100 times the estimated daily requirement has been used to treat hypoparathyroidism and vitamin D-resistant rickets. Vitamin A, likewise, has been used in pharmacologic doses to treat certain skin disorders as shown in figure 1.32 Both vitamins A and D are toxic at higher doses and may cause death.

Recommendations for the Pharmacologic Use of Vitamin E

Vitamin E, in doses 10 to 50 times the estimated daily requirement, has been recommended for the treatment of a variety of diseases including menstrual disorders, habitual abortion, burns, cyanotic congenital heart disease, angina pectoris, coronary thrombosis, peripheral vascular disease with intermittent claudication, thrombophlebitis, hypertension, rheumatic fever and rheumatic heart disease, indolent ulcers, the vascular complications of diabetes mellitus, and glomerulonephritis. Fortu-
nately, overt toxicity has not been observed in patients taking these doses over considerable periods of time. The main proponents of this pharmacologic use of vitamin E in cardiovascular disease are Drs. Evan and Wilfrid Shute and their colleagues at the Shute Institute in London, Ontario. Much of the original work by the Shutes purporting to support these recommendations were uncontrolled case studies. Evaluation of the usefulness of \( \alpha \)-tocopherol therapy in selected cardiovascular disorders will be attempted here only when two or more clinics have studied a given problem.

1) Peripheral vascular disease with intermittent claudication. The effects of vitamin E in doses of 600 to 800 I. U. per day upon intermittent claudication have been studied by a number of workers. Boyd et al. found that 40% of 71 patients with moderately severe claudication were improved with vitamin E therapy over a 6 month period. However, Baer and Heine and Hamilton et al. both reported negative results in a double blind study over a 3 month period.

In a subsequent longer study lasting 40 weeks, Livingstone and Jones reported positive results in a double blind study employing 34 patients. Seventy per cent of the vitamin E treated patients appeared to improve whereas only 10% of the patients receiving placebos improved. Because of the small sample, the difficulty of classification of patients with intermittent claudication, and the possibility of sample bias, it is difficult to evaluate these results. The authors themselves write, "Many criticisms can be applied to this study . . . it is well known that intermittent claudication will sometimes improve without any treatment." The same criticism can be applied to the study by Williams et al. who found negative results in 15 patients with aortoiliac occlusion and femoral-popliteal occlusion with good distal arteries, but improvement in 19 of 30 patients with femoral-popliteal occlusion with poor distal arteries. In the latter study, however, only 15 comparable patients received placebos and 2 of 15 improved.

2) Angina pectoris and ischemic heart disease. All reports of studies of the effect of vitamin E therapy upon angina pectoris and the course of ischemic heart disease have been negative except those from the Shute clinic. Studies by Donegan et al. from Duke University, by Rinzler et al. from Cornell University, by Ravin and Katz from Boston University, and by Makinson et al. from Manchester, England, have been negative. No convincing new information has been forthcoming from the Shute Clinic.

3) Congestive heart failure. No effects of tocopherol therapy upon the course of patients with decompensated heart disease and congestive heart failure was observed by Donegan et al. or by Levy and Boas.

4) Thrombophlebitis and thromboembolic states. The claim is made by Ochsner that \( \alpha \)-tocopherol is of preventive value in thromboembolism. We have not been able to confirm the claim that \( \alpha \)-tocopherol is an antithrombin (Kipfer RK and Olson RE, unpublished results). The report of Zierler et al. of the antithrombin activity of \( \alpha \)-tocopherol phosphate is not relevant, since the phosphate, which is an ionic detergent, is not present in the body. Furthermore, phosphate ion itself enhances antithrombin activity.

5) Other cardiovascular disorders. There has been insufficient study of the other claims made for the efficacy of vitamin E in diabetic vasculitis, glomerulonephritis, congenital heart disease, and hypertension to comment.

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